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hereby declare that I am conversant with the French and the English languages and I certify that to the best of my knowledge and belief the following is a true and correct English translation of the specification contained in French patent application n° 98 10889 filed on the August 31, 1998.

in the name of : FORCEVILLE Xavier

Signed in Paris on the January 23, 2004

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Use of selenium for treating patients suffering from systemic inflammatory response syndrome (SIRS), and composition for implementing the treatment

The present invention relates to the use of selenium for treating patients suffering from systemic inflammatory response syndrome (SIRS).

It also relates to a composition for implementing this treatment.

The role of selenium, as an oligo-element involved in many reactions in the organism, is widely known.

Thus, this element plays a major role in the intracellular antioxidant system, particularly as a component of glutathione peroxidase. In addition, selenium appears to play a direct role in the regulation of the inflammatory process.

Since the 1970's, selenium deficiency has been linked with severe cardiomyopathies, found in particular in populations living in regions of China which are deficient in selenium. The effectiveness of sodium selenite in oral form, both as a prophylactic and as a cure, against these diseases has been described.

The role of selenium in intense oxidative stress situations has been shown.

VITOUX et al. (1966, Therapeutic Uses of trace elements, Neve et al. ed., Plenum Press, New York, 127-131) have shown that the plasma concentration of selenium decreased significantly in patients admitted to intensive care units presenting a systemic inflammatory response syndrome.

However, no information was given as to the use of selenium to treat such patients.

ZIMMERMANN et al. (1997, Medizinische Klinik, 92, 3-4 suppl. III) have described, but not in detail, the results of a study on the effect of sodium selenite in patients suffering from systemic inflammatory response syndrome. In this study, the patients first received an injection of 1000 µg of sodium selenite, then 1000 µg of sodium selenite per day by continuous perfusion for twenty-eight days. The authors considered the administered dose of selenium to be optimal.

However no information was given as to the pathology of the patients treated. It is simply stated that these were patients suffering from SIRS, of which some had organ failures of unspecified nature. In addition,

ZIMMERMANN et al. mentioned that the control group had a mortality rate of 40%, which is a high figure considering the type of patient treated and the stated severity index. These figures thus have low credibility and, in addition, do not agree with other data given in this article. It is thus not possible to deduce from this article what pathologies might be treated by selenium.

Other studies describing the effect of selenium on various pathologies have been published. Thus the article of YA-JUN HU et al. (1997, Biological Trace Element Research, 56, 331-341) describes the use of selenium to reduce the toxicity of an anti-cancer product, cisplatine, in cancer patients. The patients were treated with doses of 4 mg per day of selenium, in the form of kappa-selenocarrageenan, orally.

Some of these studies show results which are conflicting and obtained on unconvincing experimental bases.

Thus, the skilled person was faced with a large number of documents stating that selenium could be used in various pathologies, but without having any real certainty as to the effect of this oligo-element, considered as toxic and pro-oxidant in the dosage regimes used in some oxidative stress situations.

Moreover some pathologies revealing a systemic inflammatory response syndrome (SIRS) are responsible for significant mortality rates, mainly in intensive care units, and severe visceral failure potentially requiring major life-support therapy.

It is thus necessary to develop a treatment which can reduce this mortality and reduce the incidence of associated visceral failures.

However, patients presenting a syndrome of the SIRS type are in a very weakened state, following an oxidative stress situation, and are considered to be poorly able to resist doses of selenium thought to be toxic, and additionally themselves pro-oxidant.

It is thus not possible for a person skilled in the art to extrapolate results obtained from patients with other pathologies to patients presenting a syndrome of the SIRS type, and to use doses of selenium considered as toxic and pro-oxidant in an oxidative stress situation.

The present invention has shown that it is possible to reduce the mortality and the incidence of visceral failures, particularly renal, respiratory, haematological (coagulation), cardiovascular, hepatic, gastro-intestinal and neurological failures resulting from a systemic inflammatory response syndrome (SIRS) by using high doses of selenium in comparison with those generally

considered to be toxic by a skilled person.

It has thus been shown that good effectiveness is obtained in the treatment of syndromes of the SIRS type by treating the patients with a drug containing during the first days of the treatment a high dose of selenium, then by reducing this dose in the subsequent treatment.

The object of the present invention is thus the use of at least one molecule containing selenium, in a quantity corresponding to a daily dose of about 2 to 40 mg, and preferably 4 to 40 mg of atomic selenium equivalent, for the production of a drug for treating severe systemic inflammatory response syndrome (SIRS), or any state corresponding to a severe acute attack of an inflammatory pathology causing an exacerbation of cytokine secretion. Particularly included in this definition are any severe acute infectious condition, whether the infection is of bacterial, fungal, viral or parasitic origin.

According to the present invention, systemic inflammatory response syndrome, or SIRS, should be understood as any pathology fulfilling the definition given by BONE et al. in 1992 during the ACCP/SCCM standardisation conference (BONE et al., 1992, Chest, 101, 1644-1655).

Preferably, the drug corresponding to a daily dose of 2 to 40 mg of atomic selenium equivalent, and preferably from 4 to 40 mg atomic selenium equivalent, is preferably administered over a short time period, at the beginning of the treatment, with the subsequent treatment using lower doses of selenium.

The object of the present invention is therefore the use of at least one molecule containing selenium for treating SIRS in a quantity corresponding to a daily dose of about 2 to 40 mg of atomic selenium equivalent, at the beginning of the treatment, then a daily dose of about 0.5 to 2 mg of atomic selenium equivalent, in the subsequent treatment.

Such a drug is preferably intended for the treatment of septic shock states such as peritonitis, pneumopathies, meningitis or bacterial septicemias.

It is also intended in general for the treatment of patients having a severe immuno-inflammatory reaction, associated with pancreatitis, extensive burns, multiple trauma, any type of septicemia, especially bacterial, but also in the context of severe parasitic, fungal or viral states, a major surgical operation, a surgical operation with clamping (ischemia-reperfusion), a state of shock whatever its etiology or type. The new drug may also be used in patients presenting a visceral failure. The patient may also be suffering from an alcoholic hepatopathy, cirrhosis, of whatever origin, anorexia,

undernourishment, malnutrition, or AIDS or a chronic inflammatory pathology, especially intestinal.

According to a preferred embodiment, the drug is produced so as to give a daily dose of about 2 to 40 mg of atomic selenium equivalent, during the first day, and optionally the second and third days of treatment.

It is also advantageously produced so as to give a daily dose of about 0.5 to 2 mg of atomic selenium equivalent for 1 to 20 days and, preferably, from 1 to 10 days during the subsequent treatment.

The molecule containing selenium may be any pharmacologically acceptable molecule. It may be a selenium salt, such as a selenite or selenate of inorganic selenium, or an organic selenium, for example selenocysteine, or selenomethionine, selenated yeasts or synthetic chemicals containing one or more atoms of selenium. It is preferably sodium selenite.

The drug is preferably prepared in an injectable or perfusable pharmaceutical form or for enteral administration. It may however be in any form which allows the administration of the molecule or molecules containing selenium and the effective treatment of the SIRS.

This drug may be administered by the parenteral route, preferably by intravenous, also by enteral routes.

This drug is preferably intended as curative. It may however be administered preventatively, particularly before a major surgical operation, especially vascular surgery, so as to limit the oxidative stress.

Such a drug or pharmaceutical composition may contain pharmaceutically acceptable excipients, in addition to the molecule or molecules containing selenium. In the form of a perfusion, it may contain between about 1.3 mg/l and 800 mg/l of atomic selenium equivalent.

Such a drug may comprise, in addition to the selenium containing molecule, also vitamin C, vitamin E or zinc, or also any other molecule allowing an antioxidant effect, while exhibiting a pharmacological compatibility with the selenium containing molecule. The addition of these vitamins or of this metal allows to potentialise the effect of selenium.

As an illustrative embodiment, a drug or a pharmaceutical composition may conatin an mount of vitamin C or of vitamin E for a daily dose comprised between 20 and 2000 mg.

As an illustrative embodiment, a drug or a pharmaceutical composition according to the invention may in addition contain zinc for a daily dose

comprised between 5 and 50 mg, or any other essential oligo-element.

The present invention is illustrated, without in any way being limited, by the following examples.

EXAMPLE 1

A patient aged 51, 75 kg, chronic alcoholic with no history of icteroascitic, hemorrhagic or encephalopathic compensation, was admitted to postoperative intensive care with generalized purulent peritonitis from colonic perforation during an attack of diverticular sigmoiditis.

His initial hemodynamics were maintained by perfusion. He was intubated-ventilated under sedation with a FiO_2, slightly increased, of 50%. There was a moderate renal insufficiency. An adapted empirical antibiotic therapy was begun, and modified after 48 hours in view of the antiobiograms. At 24 hours his severity indexes were IGS II 29, APACHE II 17 and SOFA score was 5. One day after the operation, the situation worsened rapidly with onset of a state of shock with lactic acidosis 5 µmol/l requiring administration of dopamine then rapidly noradrenaline up to 4 mg/h (0.9 µg/kg/min). There was a deterioration of his respiratory state requiring increase of the FiO_2 because of the onset of an acute adult respiratory distress syndrome (ARDS). As soon as the necessity of noradrenaline administration was recognized, a treatment with sodium selenite by continuous administration was begun at a dose of 4 mg of atomic selenium equivalent over the first 24 hours, followed by continuous administration of sodium selenite at a dose of 1 mg of atomic selenium equivalent for 10 days.

This treatment had the effect of limiting the extent of this vasoplegic shock condition, thus avoiding early death. This treatment also resulted in limiting the extent of visceral failure. The progress was marked by the outcome of a renal insufficiency with continued diuresis, but not requiring dialysis. Ventilation at FiO_2 70% was very transiently necessary because of a rapidly resolved ARDS. The administration of noradrenaline was progressively withdrawn in three days. The lactic acidosis regressed rapidly. There was no appearance of disseminated intravascular coagulation, the platelet level remaining higher than 150 000 platelets/mm^3. No postoperative nosocomial infection was observed, and in particular no nosocomial pneumopathy. Nor was there any abdominal complication. This patient left intensive care 10 days after the operation.

He returned for a consultation 3 months afterwards. He then recommenced his working career and his normal lifestyle.

EXAMPLE 2

A female patient aged 35, depressive, anorexic, 51 kg and 1.75 m tall, was admitted on a tentative diagnosis of drug-induced suicide with ingestion of a large amount of analgesics and sedatives. The diagnosis was rapidly changed to generalized purulent peritonitis from a perforated gastric ulcer. She was transferred to postoperative intensive care. There was also a shock condition requiring perfusion and introduction of catechol amines as noradrenaline and dolbutamine; lactic acidosis at 6 µmol/l. Antibacterial and antifungal antibiotic therapy was performed. Diuresis was maintained under diuretics. One hour after the start of noradrenaline administration, a treatment with sodium selenite by continuous administration was begun at a dose of 4 mg of atomic selenium equivalent over the first 24 hours, followed by continuous administration of sodium selenite at a dose of 1 mg of atomic selenium equivalent for 10 days. At 24 hours the severity indexes were IGS II 44, APACHE II 35. The SOFA score was 8.

Progress was initially favourable with regression of the shock condition in 24 hours. There were no significant visceral failures, return of diuresis (creatinine clearance at 40), ventilation FiO_2 60%, no PEP (positive expiration pressure), no coagulation problems except a platelet level of 50%. Onset of two atelectasia attacks requiring fibroaspiration. Early enteral feeding was installed.

Eight days after the operation, there was a persistence of a purulent discharge in the drains. Abdominal scanning showed a sub-hepatic gathering, without free peritoneal effusion. A puncture under scanner was performed to drain this gathering. Bacteriological tests on the free pus revealed colonies of Hafnia alvei and Candida albicans; the antibiotic therapy was modified according to the antibiogram.

Twelve days after the operation, a nosocomial pneumopathy from hemolytic alpha Streptococcus arose (diagnosed by fibroscopy with a protected telescopic brush and brochoalveolar washing). An empirical antibiotic therapy against gram positive cocci was installed, then adapted to the antibiogram. Extubation was performed 20 days after the operation. Extensive physiotherapy was necessary to avoid reintubation.

This patient was transferred to convalescent care for continuance of renutrition on the 35th day. She returned for consultation after 3 months. Her weight had risen to 56 kg. Psychotherapy was begun.

EXAMPLE 3

A patient aged 57, presenting major alcohol-tobacco addiction (more than 1 litre of wine per day, 2 packets of cigarettes per day), chronic BPCO respiratory insufficiency, stage 2 arteritis of the lower limbs and deterioration in general health for several months with a productive cough, was transferred to intensive care after a short stay in general medicine. At admission there was a respiratory distress requiring emergency intubation-ventilation. Blood gases confirmed major respiratory acidosis. The patient was feverish. There was a hyperleucocytosis of 24 000 leucocytes of which 88% were polymorphonuclear cells. Blood pressure was stable under perfusion, however there were blotches on the knees. There were no coagulation problems nor renal insufficiency. At 24 hours IGS II was 41, APACHE II 26, and SOFA score 8. Lung samples taken by protected telescopic brush and brochoalveolar washing confirmed the diagnosis of community-acquired pneumonia: 47% of cells infected, Haemophilus influenza β-lactamase negative and wild-type streptococcal anginosis. Dual antibiotic therapy was started which should prove effective against these organisms. Thoraco-abdominal scanning showed a large liquid gathering within the pulmonary parenchyma of the right lower lobe, appearing to fistulize in the pleural with pleurisy. The abdominal scan also revealed the existence of a thrombosed aneurism of the sub-renal abdominal aorta.

The immediate development was marked by a rapid deterioration of his respiratory state with necessity of ventilation at FiO_2 100%, PEP 8. In addition, very substantial perfusion was necessary with measurement of pressure by right catheterization. Dopamine had to be administered at 10 µg/kg/min. After 8 hours dopamine administration, a treatment with sodium selenite by continuous administration was begun at a dose of 4 mg of atomic selenium equivalent over the first 24 hours, followed by continuous administration of sodium selenite at a dose of 1 mg of atomic selenium equivalent for 10 days.

After increase of the dopamine to 20 µg/kg/min and addition of adrenaline at 1 mg/h, the hemodynamics seemed to stabilize. The hyperlactatemia increased in parallel up to 10 µmol/l, then reduced as from the second day. Progress towards a fatal shock condition was thus avoided. At

the respiratory level, treatment with nitrogen monoxide (NO) was started at 10 ppm. Diuresis was maintained under diuretics. There was a thrombopenia at 7500 platelets/mm^3 combined with a lengthening of the coagulation time and an increase in fibrin degradation products, indicating a moderate CIVD. Drainage of the purulent pleurisy was instituted.

As from the second day a progressive improvement of the situation was observed, both respiratory and hemodynamic. The drainage allowed complete evacuation of the pleurisy with drainage of the pulmonary abscess. The catechol amines were withdrawn on the fifth day. Extubation was performed on the sixth day. The patient was transferred back to pneumology on the fifteenth day for continuing exploration and treatment of his respiratory insufficiency.

This patient was seen in consultation 3 months afterwards. A dental abscess was treated. A return to normal work is under way. The patient does not have oxygenation at home.

These results are in agreement with those obtained over a larger series, showing a clear improvement of the prognosis of patients treated with high doses of selenium compared with those having received a placebo.

By IGS II should be understood the simplified severity index II defined by LE GALL et al. in 1993 (A New Simplified Acute Physiology Score) [SAPS II] Based on a European/North American Multicenter Study, JAMA, 1993; 270:2957-2963), by APACHE II (Acute Physiology and Chronic Health Evaluation II) the severity index defined by W.A. KNAUS et al. (APACHE II: A severity of disease classification system. Crit. Care Med. 1985; 13: 818-829), and by SOFA score, the score of visceral failure defined by J.L. VINCENT et al. (The SOFA [Sepsis-related Organ Failure Assessment] score to describe organ dysfunction/failure. Intensive Care Med. 1995; 22:707-710).

CLAIMS

1. Use of at least one molecule containing selenium, in a quantity corresponding to a daily dose of about 2 to 40 mg of atomic selenium equivalent for the manufacture of a drug for treating severe systemic inflammatory response syndrome or any state corresponding to a severe acute attack of an inflammatory pathology causing an exacerbation of cytokine secretion.

2. Use of at least one molecule containing selenium for the production of a drug for treating systemic inflammatory response syndrome, in a quantity corresponding to a daily dose of about 2 to 40 mg of atomic selenium equivalent, at the beginning of the treatment, then at a daily dose of about 0.5 to 2 mg of atomic selenium equivalent, in the subsequent treatment.

3. Use according to one of claims 1 or 2 in which the drug is intended for treating severe acute infectious states, such as peritonitis, pneumopathies, meningitis or bacterial septicemias in a septic shock state.

4. Use according to any one of claims 2 and 3, cahracterised in that the drug is manufactured for providing a daily dose of from about 2 to about 40 mg atomic selenium equivalent during the first day and eventually during the second day and the third day of treatment.

5. Use according to any one of claims 2 to 4 in which the drug is produced so as to give a daily dose of about 0.5 to 2 mg of atomic selenium equivalent, for 1 to 20 days during the subsequent treatment.

6. Use according to any one of claims 1 to 5 according to which one of the molecules containing selenium is sodium selenite.

7. Use according to any one of claims 1 to 6, characterized in that the drug is in an injectable or perfusable pharmaceutical form or for enteral administration.

8. Use according to any one of claims 1 to 7, characterized in that the drug contains vitamin C or vitamin E.

9. Use according to any one of claims 1 to 8, characterized in that the drug contains zinc or any other essential oligo-element.

10. Pharmaceutical composition characterized in that it comprises a quantity of molecule or molecules containing selenium corresponding to a daily dose of about 2 to 40 mg of atomic selenium equivalent, and pharmaceutically acceptable excipients.

11. Pharmaceutical composition according to claim 10, characterized in that it contains vitamin E or vitamin C.

12. Pharmaceutical composition according to any one of claims 10 and 11, characterized in that it contains zinc.

13. Composition according to any one of claims 10 to 12, characterized in that it is in an injectable or perfusable form or for enteral administration.

14. Composition according to any one of claims 10 to 13, characterized in that it is in the form of a perfusion containing between about 1.3 and 800 mg of atomic selenium equivalent per litre.